# Hyperglycemia and Death in Cystic Fibrosis–Related Diabetes

Amanda I. Adler, MD, PHD[1,2]
Brian Shine, MD[3]
Charles Haworth, MD[2]
Lalantha Leelarathna, MRCP[1]
Diana Bilton, MD[4]

**OBJECTIVE**—Diabetes is common in cystic fibrosis and increases the risk of death, yet the role of hyperglycemia remains unproven. An association between glycemia and mortality would provide compelling evidence to support glucose lowering in cystic fibrosis–related diabetes (CFRD).

**RESEARCH DESIGN AND METHODS**—Using the U.K. Cystic Fibrosis Registry, we analyzed longitudinal data from 2006 to 2009 in 520 individuals with diabetes. We tested the association between $HbA_{1c}$ and mortality.

**RESULTS**—During a median follow-up of 2 years, 36 patients died. The median value of $HbA_{1c}$ was higher in those who died (7.3%) than in those who did not (6.7%). An $HbA_{1c}$ value of ≥6.5% was associated with a threefold increased risk of death (hazard ratio 3.2 [95% CI 1.4–7.3]; $P = 0.005$) independent of potential confounders.

**CONCLUSIONS**—Hyperglycemia trebles the risk of death in patients with CFRD. These findings provide epidemiologic support for continued efforts to improve glycemic control.

*Diabetes Care* 34:1577–1578, 2011

Diabetes frequently complicates cystic fibrosis. Cystic fibrosis–related diabetes (CFRD) has an incidence in teenagers of up to 6% per year and a prevalence in adults of >30% (1,2). Diabetes further elevates the already high mortality rates in cystic fibrosis (3–5). In individuals without cystic fibrosis, diabetes increases the risk of death, and in individuals with diabetes, hyperglycemia increases the risk of death (6,7). However, no study of CFRD using national data has investigated whether hyperglycemia, per se, increases the risk of death; likewise, no trial has tested whether controlling blood glucose prolongs survival. Proving an association between glycemia and mortality in cystic fibrosis would provide compelling observational evidence to inform clinical practice. Using the U.K. Cystic Fibrosis Registry, we performed longitudinal analyses to test the association between glycemia, as measured by $HbA_{1c}$, and mortality in individuals with CFRD.

## RESEARCH DESIGN AND METHODS

The U.K. Cystic Fibrosis Registry collects clinical data from cystic fibrosis specialist clinics around the U.K. Since 2006, the U.K. Cystic Fibrosis Registry has recorded $HbA_{1c}$. We performed survival analyses for individuals with diabetes from the first clinical visit in 2006 to the time of death or censoring (1 August 2009). Diabetes was defined by physician diagnosis and/or oral glucose tolerance testing with values of 7 mmol/L fasting or 11.1 mmol/L at 2 h. Of 5,810 individuals who had clinical reviews from 2006 onward, we analyzed data from 520 of 912 individuals with diabetes for whom full clinical data, including at least one measurement of $HbA_{1c}$, were available. $HbA_{1c}$ was measured in local, accredited National Health Service laboratories.

We tested the association between glycemia, measured at the first clinical visit (baseline) and categorized as an $HbA_{1c}$ ≥6.5 vs. <6.5%, and mortality. An $HbA_{1c}$ value of 6.5% approximates the median value and reflects excellent glycemic control. Potential confounders, previously identified as plausibly related to both the incidence of diabetes and mortality (1,3) and measured at baseline, included age; sex; BMI *z* score; pulmonary function, as measured by percent predicted forced expiratory volume at 1 s ($FEV_1$); and use of corticosteroids (either oral or inhaled). The registry did not provide information on duration of diabetes. We measured time to event from registration to death or censoring and modeled the data using proportional hazards regression with $HbA_{1c}$ as the main exposure variable in univariate and multivariate models. Death was the dependent variable.

## RESULTS

The median age of patients was 25.0 years (range 0.4–67.8), and $HbA_{1c}$ was 6.7% (4.9–17.0). A total of 84% of patients received treatment to lower blood glucose. Patients with $HbA_{1c}$ values ≥6.5%, relative to those with values <6.5%, did not differ significantly with respect to age, sex, BMI, pulmonary function, or use of corticosteroids. During a median follow-up of 2.01 years (0.02–3.53), 36 patients died. The median value of $HbA_{1c}$ was higher in those who died (7.3%) than in those who did not (6.7%) (Table 1). Table 1 contrasts the characteristics of the patients who died with those who did not. An $HbA_{1c}$ value of ≥6.5% was associated with a threefold increased risk of death (hazard ratio 3.2 [95% CI 1.4–7.3]; $P = 0.005$). The association did not change when controlling for risk factors for death conceivably related to hyperglycemia (age, sex, BMI *z* score, $FEV_1$, and use of corticosteroids). In multivariate analysis, $HbA_{1c}$ ≥6.5% was associated with a hazard ratio of 3.3 (95% CI 1.4–7.5; $P = 0.005$).

Respiratory disease was the number one cause of death. Among those who died, the proportion who died from respiratory disease did not differ between those with $HbA_{1c}$ values >6.5 or <6.5%, comprising 20 of 29 (69%) deaths in individuals with $HbA_{1c}$ values at or above 6.5% and 4 of 7 (57%) deaths in individuals with lower values.

From the [1]Wolfson Diabetes and Endocrine Clinic, Addenbrooke's Hospital, Cambridge, U.K.; the [2]Adult Cystic Fibrosis Centre, Papworth Hospital, Cambridge, U.K.; the [3]Department of Clinical Biochemistry, John Radcliffe Hospital, Oxford, U.K.; and the [4]Adult Cystic Fibrosis Clinic, Royal Brompton Hospital, London, U.K.
Corresponding author: Amanda I. Adler, amanda.adler@addenbrookes.nhs.uk.
Received 11 December 2010 and accepted 5 April 2011.
DOI: 10.2337/dc10-2289

**Table 1—*Characteristics of patients with CFRD by survival***

| Characteristic | Alive | Dead | *P* |
|---|---|---|---|
| *n* | 484 | 36 | |
| Age (years) | 26.6 ± 9.5 | 28.8 ± 9.6 | 0.18 |
| Female (%) | 44.2 | 58.3 | 0.14 |
| $HbA_{1c}$ (%) | 6.6 (5.9–7.9) | 7.3 (6.6–8.3) | 0.009* |
| BMI *z* score | −0.35 ± 1.18 | −1.14 ± 1.21 | <0.001 |
| $FEV_1$ (% predicted) | 54.3 ± 22.7 | 33.4 ± 19.5 | <0.001 |
| Using prednisolone (%) | 19.0 | 27.8 | 0.29 |

Data are means ± SD or median (interquartile range), unless otherwise indicated. *Tested using the Kruskal-Wallis one-way ANOVA.

**CONCLUSIONS**—This study shows that among individuals with cystic fibrosis and diabetes, those with $HbA_{1c}$ levels above the clinically defined target of 6.5% are more likely to die than those with lower values, an observation not accounted for by established risk factors for death. Whereas diabetes in cystic fibrosis is known to increase the risk of death, hyperglycemia in cystic fibrosis–related diabetes is not. We are not aware of another study that has shown an association between $HbA_{1c}$, a validated measure of glycemia in cystic fibrosis (8), and death. In Minnesota, of adults with CFRD, more patients who developed fasting hyperglycemia died during the study period (26% [*n* = 8]) compared with 7% (*n* = 6) of patients who did not develop fasting hyperglycemia, suggesting a role for hyperglycemia (5).

In a few individuals, an elevated $HbA_{1c}$ value may have reflected their illness and impending death. There were too few individuals who died within months of measuring their $HbA_{1c}$ to test this possibility. In addition, other factors may have confounded the findings of this study. However, we observed no change in the magnitude of the increase in risk associated with hyperglycemia when taking into account well established risks for morbidity in cystic fibrosis. It also is possible, given the median value of $HbA_{1c}$, that some included individuals did not have diabetes. Nonetheless, it is likely that they had dysglycemia, and, in any event, this misclassification would have minimally biased our findings.

Excluded from this study were a substantial proportion of individuals who had diabetes but who did not have available values of $HbA_{1c}$ and other clinical data. Of note, included individuals were not more likely to die than excluded individuals (data not shown). Our results, therefore, are likely generalizable.

This study shows that the increased mortality with hyperglycemia occurs for respiratory disease, which is not classically considered a complication of diabetes. The many potential mechanisms may include poorer nutrition, greater catabolism, and higher risks of infection. In cystic fibrosis, blood glucose values correlate with airway glucose concentrations, and these increase the probability of colonization with pathogens (9).

No randomized trial has yet addressed glucose lowering in cystic fibrosis with the a priori outcome of extending life. In the absence of trials, this report provides epidemiologic support for continued efforts to improve glycemic control in CFRD.

**Acknowledgments**—No potential conflicts of interest relevant to this article were reported.

A.I.A. coordinated the project, designed and interpreted the analyses, and wrote the article. B.S. designed the analysis, analyzed and interpreted data, and reviewed and edited the manuscript. C.H. reviewed and edited the manuscript. L.L. interpreted data and presented the article. D.B. coordinated data and reviewed and edited the manuscript.

Parts of this study were presented in abstract form at the 70th Scientific Sessions of the American Diabetes Association, Orlando, Florida, 25–29 June 2010.

The authors thank the U.K. Cystic Fibrosis Trust Clinical Teams who contributed data to the U.K. Cystic Fibrosis Registry.

**References**

1. Adler AI, Shine BS, Chamnan P, Haworth CS, Bilton D. Genetic determinants and epidemiology of cystic fibrosis-related diabetes: results from a British cohort of children and adults. Diabetes Care 2008; 31:1789–1794
2. Adler AI, Gunn E, Haworth CS, Bilton D. Characteristics of adults with and without cystic fibrosis-related diabetes. Diabet Med 2007;24:1143–1148
3. Chamnan P, Shine BS, Haworth CS, Bilton D, Adler AI. Diabetes as a determinant of mortality in cystic fibrosis. Diabetes Care 2010;33:311–316
4. Liou TG, Adler FR, Cox DR, Cahill BC. Lung transplantation and survival in children with cystic fibrosis. N Engl J Med 2007;357:2143–2152
5. Milla CE, Billings J, Moran A. Diabetes is associated with dramatically decreased survival in female but not male subjects with cystic fibrosis. Diabetes Care 2005;28: 2141–2144
6. Stadler M, Auinger M, Anderwald C, et al. Long-term mortality and incidence of renal dialysis and transplantation in type 1 diabetes mellitus. J Clin Endocrinol Metab 2006;91:3814–3820
7. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405–412
8. Brennan AL, Gyi KM, Wood DM, Hodson ME, Geddes DM, Baker EH. Relationship between glycosylated haemoglobin and mean plasma glucose concentration in cystic fibrosis. J Cyst Fibros 2006;5:27–31
9. Brennan AL, Gyi KM, Wood DM, et al. Airway glucose concentrations and effect on growth of respiratory pathogens in cystic fibrosis. J Cyst Fibros 2007;6:101–109